SmithKline Beecham
Pharmaceuticals

8090 '99 APR 19 A11:46

April 15, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: **[Docket No. 99D-0121]** ***Draft Guidance for Industry on Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Containing Certain Active Moieties/ Active Ingredients Based on a Biopharmaceutics Classification System*** **(January 1999 Draft)**

Dear Madam or Sir:

SmithKline Beecham Pharmaceuticals appreciates the opportunity of providing comments on the above-captioned draft guidance which provides a framework for requesting a waiver of *in vivo* bioavailability (BA) and/or bioequivalence (BE) studies (biowaivers) for certain immediate release solid oral dosage forms based on a Biopharmaceutics Classification System.

Our comments on specific issues begin on the following page. They are listed by section, page number, and location of the paragraph and line corresponding to the draft guidance.

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709 Swedeland Road, PO Box 1539, King of Prussia, PA 19406-0939. Telephone (610) 270 4800. Fax (610) 270 7777.

Page #	Location	Comment:
SECTION II. BACKGROUND		
2	para 2, line 1	"...not based on *in vivo* methods...." The guidance does describe *in vivo* methods which can be used in requesting a biowaiver.
2	para 2, line 5	"For such products, in vivo demonstration of bioequivalence may not be necessary because the BA/BE of a drug product so characterized approaches that of a solution and is thus self-evident (21 CFR 320.22(b) (3)". This statement indicates that if a drug has high solubility and dissolves rapidly bioequivalence between dosage forms is self evident and is independent of its permeability. 21 CFR 320.22(b) indicates a waiver can be granted for oral solutions, elixirs, tinctures or similar other solubilized forms without reference to drug permeability. In a recent publication by Kaus et al (Pharm Res 16, 272, 1999), the authors demonstrate that the Cmax values of high permeability drugs are more sensitive to changes in dissolution rate and gastric emptying than are low permeability drugs. Based on this information, it is recommended that the Guidance be extended to all high solubility drugs independent of permeability.
2	para 2, line 9	"...as long as its inactive ingredients do not significantly affect absorption of the active ingredients..." Does the Agency intend to provide a list of inactive ingredients that significantly affect absorption?
SECTION III. THE BIOPHARMACEUTICS CLASSIFICATION SYSTEM		
3	Part A, line 3	"....over the pH range of 1-8..." The pH range of 1 -8 cited in this Guidance is at variance with contemporary scientific literaure which indicates that intestinal pH is considerably lower that pH 8. The USP has recently lowered the pH of Simulated Intestinal Fluid from 7.5 to 6.8 and the FDA Guidance on Dissolution Testing of Immediate Release Solid Oral Dosage Forms recommends dissolution media in the pH range 1.2 to 6.8. It is recommended that the Guidance be modified to refer to a pH range 1 to 6.8.

Page #	Location	Comment:
SECTION IV. METHODOLOGY FOR CLASSIFYING A DRUG		
4	Part A, para 1, line 3	"...eight or more pH..." The reference to eight or more pH values seems to be too prescriptive. If a drug has no pKa in the pH range this recommendation makes little sense. It is recommended that the wording be modified to read "Solubility should be determined at a sufficient number of pH values to accurately define the pH - solubility profile."
4	Part A, para 2, line 4	What other ionization characteristics in addition to pKa(s) are being referred to?
4	Part B, para 1, lines 3-5	It is not clear what supportive information will be derived from octanol:water partition coefficient or other physical-chemical properties? It is recommended that this request for supportive data be removed from the Guidance.
4	Part B.1, line 4	"...(e.g., six or more)..." The reference to six or more is too prescriptive. It is recommended that the wording be changed to " Sufficient number of subjects, considering the variability of the compound, which may be as few as 3 - 4 subjects for compounds with low variability..."
5	Part B.2, para 1, line 6	"...cultured human intestinal cells..." It does not matter what cell line is used as long as the appropriate controls and validation have been conducted. It is recommended that "cultured human intestinal cells" be replaced with "cultured intestinal cells."
5	Part B.2, para 2, line 3	"...established using 20 or more selected...." The reference to 20 compounds is too prescriptive. There are not even 20 compounds listed in the Attachment.
6	Part B.2, para 4, line 8-10	"...(2) a linear relationship..." This statement does not relate to *in vitro* permeability/methods and should be omitted from this discussion.

Page #	Location	Comment:
6	Part B.2, para 4, line 12	"...and 10 times..." Frequently it will not be possible to evaluate permeability at a concentration which is 10 times the dose. It is recommended that an acceptable approach would be to evaluate the permeability over 3 log units with the highest concentration being the highest dose strength dissolved in 250 ml.
6	Part B.2, para 4, line 14	There are no criteria for a "similar" rate of transport.
SECTION V. REQUESTING A WAIVER OF IN VIVO BA/BE STUDIES		
6	Part 3, line 3	"...exhibit *similar* dissolution..." It is recommended that this phrase be changed to "...exhibit *faster or similar* dissolution...."
SECTION VI. ADDITIONAL CONSIDERATIONS WHEN PLANNING A REQUEST FOR A WAIVER		
7	Part A, line 9	"...pH range of 1-8..." It is recommended that the pH range be changed to "...pH 1-6.8...".
7	Part A, line 12	"...about three hours..." What is the basis for this recommendation? Is there data to support this time period?
8	Part B, last 2 lines	"...a brief summary....." This part of the sentence does not seem to fit with the rest of the paragraph. Perhaps this statement should be added to Section V as number 7.
8	Part C, lines 3-4	The reference to consulting the review division suggests a possible division-by-division interpretation to the BCS. The Agency is encouraged to adopt a consistent application of the BCS.

Page #	Location	Comment:
SECTION VII. REGULATORY APPLICATION OF THE BCS		
9	Part A.1, para 1, line 2	"...with in vivo BA documented" Does this phrase mean in comparison to an oral solution or are there other possibilities?
9	Part B, line 5	"Where feasible,..." Omit "Where feasible"
10	Part C, line 8	"...of the postchange product..." This phrase does not seem to belong with the remainder of the sentence.
10	Part C, line 10	"...as defined..." Where is this defined?

Again, thank you for the opportunity of commenting on these issues. If you have any questions, please contact me at (610) 270-6017.

Sincerely,

Robin S. Roman, Ph.D., Director
Pharmaceutical Development

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